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L1 167801 TRANSGENIC

=> s l1 and mice

L2 97406 L1 AND MICE

=> s l2 and CTGF

L3 12 L2 AND CTGF

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L4 5 DUP REMOVE L3 (7 DUPLICATES REMOVED)

=> d l4 1-5 cbib abs

L4 ANSWER 1 OF 5 MEDLINE

DUPLICATE 1

2001216125 Document Number: 21134299. PubMed ID: 11237711.

Overexpression

of connective tissue growth factor/hypertrophic chondrocyte-specific gene product 24 decreases bone density in adult **mice** and induces dwarfism. Nakanishi T; Yamaai T; Asano M; Nawachi K; Suzuki M; Sugimoto

T;

Takigawa M. (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Okayama, 700-8525, Japan. ) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Mar 2) 281 (3) 678-81.

Journal

code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Connective tissue growth factor/hypertrophic chondrocyte-specific gene product 24 (**CTGF**/Hcs24) is a multifunctional growth factor for fibroblasts, chondrocytes, and vascular endothelial cells. In the present study, we established **transgenic** (Tg) **mice** that overproduce **CTGF**/Hcs24 under the control of mouse type XI collagen promoter. Tg **mice** could develop and their embryonic and neonatal growth occurred normally. But they showed dwarfism within a few months of birth. X-ray analysis revealed that their bone density was decreased compared with normal **mice**. The femurs in the hindlimbs in particular showed an apparent low density. These results indicated that

overexpression of **CTGF**/Hcs24 affects certain steps of endochondral ossification. In addition, the testes were much smaller than normal and fertility was affected in Tg **mice**, indicating that **CTGF**/Hcs24 may also regulate the embryonic development of the testis. Copyright 2001 Academic Press.

L4 ANSWER 2 OF 5 SCISEARCH COPYRIGHT 2001 ISI (R)

2000:356797 The Genuine Article (R) Number: 311EJ. Increased expression of connective tissue growth factor in fibrotic human liver and in activated hepatic stellate cells. Williams E J (Reprint); Gaca M D A; Brigstock D

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R; Arthur M J P; Benyon R C. UNIV SOUTHAMPTON, SOUTHAMPTON GEN HOSP, D LEVEL, S ACAD BLOCK, SOUTHAMPTON SO16 6YD, HANTS, ENGLAND (Reprint); OHIO STATE UNIV, DEPT SURG, COLUMBUS, OH 43210; OHIO STATE UNIV, DEPT MED BIOCHEM, COLUMBUS, OH 43210; CHILDRENS HOSP, DEPT SURG, COLUMBUS, OH 43205

JOURNAL OF HEPATOLOGY (MAY 2000) Vol. 32, No. 5, pp. 754-761.

Publisher:

MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN,

DENMARK. ISSN: 0168-8278. Pub. country: ENGLAND; USA. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Background/Aims: Connective tissue growth factor is a recently described mitogenic protein implicated in a variety of fibrotic disorders,

Connective tissue growth factor may be a downstream mediator of the pro-fibrotic and mitogenic actions of transforming growth factor-beta, promoting extracellular matrix deposition and fibrogenesis. As transforming growth factor-beta is considered important to the pathogenesis of hepatic fibrosis, we examined the possible contribution of

connective tissue growth factor to this process,

Methods: Connective tissue growth factor expression was examined in normal and fibrotic human and rat livers using RT-PCR and ribonuclease protection assays, and in primary cultures of rat hepatic stellate cells by Northern and Western blotting,

Results: Ribonuclease protection assays demonstrated connective tissue growth factor mRNA was increased 3-5-fold in human fibrotic liver compared

with normal, RT-PCR showed this mRNA was increased in carbon-tetrachloride-

treated rat liver, Northern analysis showed connective tissue growth factor mRNA was increasingly expressed during progressive activation of cultured rat hepatic stellate cells, Western analysis confirmed that freshly isolated hepatic stellate cells secreted relatively little connective tissue growth factor compared with hepatic stellate cells activated in culture, Hepatic stellate cells stimulated with transforming growth factor-beta 1 showed increased expression of connective tissue growth factor mRNA and protein,

Conclusions: Connective tissue growth factor mRNA is consistently upregulated in human liver cirrhosis of various aetiologies, supporting a role for this growth factor in hepatic fibrogenesis, Our studies suggest that hepatic stellate cells may be an important source of hepatic connective tissue growth factor in vivo, particularly following stimulation with transforming growth factor-beta.

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2001 ACS

1999:460440 Document No. 131:101260 Monoclonal antibody against connective tissue growth factor and medicinal uses thereof. Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183

19981215.

AB Disclosed is a human monoclonal antibody useful for remedying various diseases caused by human connective tissue growth factor (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various monoclonal antibodies having various characteristics against various mammalian connective tissue growth factors (mCTGFs) useful for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The **CTGF**-assocd. diseases include cell proliferation-accompanying diseases of or fibrosis of lung, hear, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, human **CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal antibody in rabbits. Similarly, monoclonal anti-hCTGF and mouse **CTGF** antibodies and producing hybridomas were prepd. Prepd. antibodies were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in **mice** model. Mol. cloning of prepd. human monoclonal anti-hCTGF antibody was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prepd. antibodies and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2001 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor.

Takigawa,

Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388 19980904.

AB A medicinal compn. contg. an antibody having a reactivity with human **CTGF** (connective tissue growth factor) has been found out to inhibit the proliferation and migration of vascular endothelial cells

and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic retinopathy, arteriosclerosis, arterial reconstriction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation or metastasis of tumor, and inflammation in various organs). Thus, recombinant human **CTGF** was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit monoclonal anti-human **CTGF** antibody was prepd. using CEADLEEIK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., **transgenic mice** were used for raising human monoclonal anti-human **CTGF** antibodies and hybridomas producing them.

L4 ANSWER 5 OF 5 MEDLINE

DUPLICATE 2

1999438098 Document Number: 99438098. PubMed ID: 10506580. Connective tissue growth factor mediates transforming growth factor beta-induced collagen synthesis: down-regulation by cAMP. Duncan M R; Frazier K S; Abramson S; Williams S; Klapper H; Huang X; Grotendorst G R. (Department of Cell Biology and Anatomy, University of Miami School of Medicine, Miami, Florida 33136, USA. ) FASEB JOURNAL, (1999 Oct) 13 (13) 1774-86. Journal code: FAS; 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a cysteine-rich peptide synthesized and secreted by fibroblastic cells after activation with transforming growth factor beta (TGF-beta) that acts as a downstream mediator of TGF-beta-induced fibroblast proliferation. We performed in vitro and in vivo studies to determine whether **CTGF** is also essential for TGF-beta-induced fibroblast collagen synthesis. In vitro studies with normal rat kidney (NRK) fibroblasts demonstrated **CTGF** potently induces collagen synthesis and transfection with an antisense **CTGF** gene blocked TGF-beta stimulated collagen synthesis. Moreover, TGF-beta-induced collagen synthesis in both NRK and human foreskin fibroblasts was effectively blocked with specific anti-**CTGF** antibodies and by suppressing TGF-beta-induced **CTGF** gene expression by elevating intracellular cAMP levels with either membrane-permeable 8-Br-cAMP or an adenylyl cyclase activator, cholera toxin (CTX). cAMP also inhibited collagen synthesis induced by **CTGF** itself, in contrast to its previously reported lack of effect on **CTGF**-induced DNA synthesis. In animal assays, CTX injected intradermally in **transgenic mice** suppressed TGF-beta activation of a human **CTGF** promoter/lacZ reporter transgene. Both 8-Br-cAMP and CTX blocked TGF-beta-induced collagen deposition in a wound chamber model of fibrosis in rats. CTX also reduced dermal granulation tissue fibroblast population increases induced by TGF-beta in neonatal **mice**, but not increases induced by **CTGF** or TGF-beta combined with **CTGF**. Our data indicate that **CTGF** mediates TGF-beta-induced fibroblast collagen synthesis and that in vivo blockade of **CTGF** synthesis or action reduces TGF-beta-induced granulation tissue formation by inhibiting both collagen synthesis and fibroblast accumulation.

=> s CTGF

L5 740 CTGF

=> s 15 and rat

L6 168 L5 AND RAT

=> s 16 and polypeptide

L7 9 L6 AND POLYPEPTIDE

=> dup remove 17

PROCESSING COMPLETED FOR L7

L8 3 DUP REMOVE L7 (6 DUPLICATES REMOVED)

=> d 18 1-3 cbib abs

L8 ANSWER 1 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1  
2001169662 EMBASE Cyclosporine induces myocardial connective tissue growth  
factor in spontaneously hypertensive **rats** on high-sodium diet.  
Finckenberg P.; Lassila M.; Inkinen K.; Pere A.-K.; Krogerus L.; Lindgren  
L.; Mervaala E.; Vapaatalo H.; Nurminen M.-L.; Ahonen J.. Dr. J. Ahonen,  
Research Laboratory, Fourth Department of Surgery, Helsinki University  
Hospital, Kasarmikatu 11-13 FIN-00130 Helsinki, Finland. Transplantation  
71/7 (951-958) 15 Apr 2001.

Refs: 69.

ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language:  
English. Summary Language: English.

AB The introduction of cyclosporine (CsA) has led to an improvement in the  
prognosis of solid organ transplantation. However, drug-induced  
hypertension and nephrotoxicity, associated with the development of  
atherosclerosis and coronary heart disease, still worsen the long-term  
outcome of CsA-treated patients. Whether the CsA-induced myocardial  
changes are associated with the induction of connective tissue growth  
factor (**CTGF**), a recently found **polypeptide** implicated  
in extracellular matrix synthesis, is not known. Methods. Spontaneously  
hypertensive **rats** (8-9 weeks old) were treated with CsA (5  
mg.ovrhdot.kg(-1).ovrhdot.d(-1) subcutaneously) for 6 weeks. The  
influence

of angiotensin-converting enzyme inhibition (enalapril 30  
mg.ovrhdot.kg(-1).ovrhdot.d(-1) orally) and angiotensin-1 receptor  
blockade (valsartan 3 and 30 mg.ovrhdot.kg(-1).ovrhdot.d(-1) orally) on  
CsA toxicity was also investigated. Myocardial morphology was examined,  
and vascular lesions were scored. Localization and the quantitative  
expression of **CTGF**, as well as collagen I and collagen III, mRNA  
were evaluated by in situ hybridization and Northern blot. Results.  
CsA-induced hypertension and nephrotoxicity were associated with  
myocardial infarcts and vasculopathy of the coronary arteries. CsA  
increased myocardial **CTGF**, collagen I, and collagen III mRNA  
expressions by 91%, 198%, and 151%, respectively. **CTGF** mRNA  
expression colocalized with the myocardial lesions. Blockade of the  
renin-angiotensin system prevented vascular damage and the CsA-induced  
**CTGF**, collagen I, and collagen III mRNA overexpressions in the  
heart. Conclusions. CsA increases **CTGF**, collagen I, and collagen  
III mRNA expressions in the heart. The induction of **CTGF** gene is  
mediated, at least in part, by angiotensin II.

L8 ANSWER 2 OF 3 MEDLINE DUPLICATE 2  
1999287915 Document Number: 99287915. PubMed ID: 10358067.

Identification

and cloning of a connective tissue growth factor-like cDNA from human  
osteoblasts encoding a novel regulator of osteoblast functions. Kumar S;  
Hand A T; Connor J R; Dodds R A; Ryan P J; Trill J J; Fisher S M; Nuttall  
M E; Lipshutz D B; Zou C; Hwang S M; Votta B J; James I E; Rieman D J;  
Gowen M; Lee J C. (Department of Bone and Cartilage Biology, SmithKline  
Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA..  
Sanjay\_Kumar@sbphrd.com) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jun 11)  
274 (24) 17123-31. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub.  
country: United States. Language: English.

AB We have identified and cloned a novel connective tissue growth  
factor-like

(**CTGF**-L) cDNA from primary human osteoblast cells encoding a  
250-amino acid single chain **polypeptide**. Murine **CTGF**-L

cDNA, encoding a **polypeptide** of 251 amino acids, was obtained from a murine lung cDNA library. **CTGF-L** protein bears significant identity ( approximately 60%) to the CCN (**CTGF**, Cef10/Cyr61, Nov) family of proteins. **CTGF-L** is composed of three distinct domains, an insulin-like growth factor binding domain, a von Willebrand Factor type C motif, and a thrombospondin type I repeat. However, unlike **CTGF**, **CTGF-L** lacks the C-terminal domain implicated in dimerization and heparin binding. **CTGF-L** mRNA ( approximately 1.3 kilobases) is expressed in primary human osteoblasts, fibroblasts, ovary, testes, and heart, and a approximately 26-kDa protein is secreted from primary human osteoblasts and fibroblasts.

In situ hybridization indicates high expression in osteoblasts forming bone, discrete alkaline phosphatase positive bone marrow cells, and chondrocytes. Specific binding of <sup>125</sup>I-labeled insulin-like growth factors

to **CTGF-L** was demonstrated by ligand Western blotting and cross-linking experiments. Recombinant human **CTGF-L** promotes the adhesion of osteoblast cells and inhibits the binding of fibrinogen to integrin receptors. In addition, recombinant human **CTGF-L** inhibits osteocalcin production in **rat** osteoblast-like Ros 17/2.8 cells. Taken together, these results suggest that **CTGF-L** may play an important role in modulating bone turnover.

L8 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2001 ISI (R)

97:207814 The Genuine Article (R) Number: WL824. Therapeutic approaches to organ fibrosis. Franklin T J (Reprint). ZENECA PHARMACEUT, ALDERLEY PK, MACCLESFIELD SK10 4TG, CHESHIRE, ENGLAND (Reprint). INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY (JAN 1997) Vol. 29, No. 1, pp. 79-89. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB. ISSN: 1357-2725. Pub. country: ENGLAND. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Scarring of superficial tissues and chronic fibroses of major organs present major medical problems ranging from disfigurement to progressive disability and death. Growing understanding of the cellular and molecular events, which are common to these intractable disorders, now provides a favourable basis for the development of effective drug therapies. Much attention is focussed on the roles of the many cytokines and growth factors, which contribute to the fibrogenic process. The transforming growth factor (TGF)-beta 1 and 2 isoforms are among the most significant of these and approaches to control their activity include blocking the activation of latent TGF-beta, preventing the ligand-receptor interactions

and the inhibition of down-stream signal transduction. Concerns regarding possible risks of the long-term suppression of TGF-beta function point to connective tissue growth factor (**CTGF**) as a possible alternative target. **CTGF** is induced by and appears to mediate at least some of the fibrogenic actions of TGF-beta, although not its important antimitogenic activity on epithelial cells. The fibrogenic effects of endothelins and angiotensin II have aroused considerable interest in the anti-fibrotic potential of antihypertensive agents designed primarily to limit the vasoconstrictive activities of these peptides.

**Polypeptides** including interferons alpha and gamma, relaxin, TGF-beta 3 and hepatocyte growth factor, all show an ability to limit fibrogenesis in either clinical or experimental situations. Finally, inhibitors of the enzymes required for the post-translational processing of collagens, including prolyl 4-hydroxylase, C-proteinase and lysyl

oxidase provide a more direct means of reducing the deposition of fibrillar collagens into the extracellular matrix although the potentially adverse effects of sustained manipulation of collagen metabolism remain to be investigated. (C) 1997 Elsevier Science Ltd.

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L3 12 S L2 AND CTGF  
L4 5 DUP REMOVE L3 (7 DUPLICATES REMOVED)  
L5 740 S CTGF  
L6 168 S L5 AND RAT  
L7 9 S L6 AND POLYPEPTIDE  
L8 3 DUP REMOVE L7 (6 DUPLICATES REMOVED)

=> s l5 and human

L9 452 L5 AND HUMAN

=> dup remove l9

PROCESSING COMPLETED FOR L9

L10 159 DUP REMOVE L9 (293 DUPLICATES REMOVED)

=> s l10 and transgenic

L11 7 L10 AND TRANSGENIC

=> dup remove l11

PROCESSING COMPLETED FOR L11

L12 7 DUP REMOVE L11 (0 DUPLICATES REMOVED)

=> d l12 1-7 cbib abs

L12 ANSWER 1 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)

2001:234345 The Genuine Article (R) Number: 409XJ. Overexpression of connective tissue growth factor hypertrophic chondrocyte-specific gene product 24 decreases bone density in adult mice and induces dwarfism. Nakanishi T; Yamaai T; Asano M; Nawachi K; Suzuki M; Sugimoto T; Takigawa M (Reprint). Okayama Univ, Dept Biochem & Mol Dent, Okayama 7008525, Japan

Japan

(Reprint); Okayama Univ, Dept Oral Anat 2, Okayama 7008525, Japan;

Kumamoto Univ, Ctr Anim Resources & Dev, Kumamoto 8600811, Japan.

BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (2 MAR 2001) Vol.

281,

No. 3, pp. 678-681. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN

DIEGO, CA 92101-4495 USA. ISSN: 0006-291X. Pub. country: Japan. Language: English.

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L12 ANSWER 2 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)

2000:356797 The Genuine Article (R) Number: 311EJ. Increased expression of connective tissue growth factor in fibrotic **human** liver and in activated hepatic stellate cells. Williams E J (Reprint); Gaca M D A; Brigstock D R; Arthur M J P; Benyon R C. UNIV SOUTHAMPTON, SOUTHAMPTON

GEN

HOSP, D LEVEL, S ACAD BLOCK, SOUTHAMPTON SO16 6YD, HANTS, ENGLAND (Reprint); OHIO STATE UNIV, DEPT SURG, COLUMBUS, OH 43210; OHIO STATE UNIV, DEPT MED BIOCHEM, COLUMBUS, OH 43210; CHILDRENS HOSP, DEPT SURG, COLUMBUS, OH 43205. JOURNAL OF HEPATOLOGY (MAY 2000) Vol. 32, No. 5, pp. 754-761. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX

2148,

DK-1016 COPENHAGEN, DENMARK. ISSN: 0168-8278. Pub. country: ENGLAND;

USA.

Language: English.

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Methods: Connective tissue growth factor expression was examined in normal and fibrotic **human** and rat livers using RT-PCR and ribonuclease protection assays, and in primary cultures of rat hepatic stellate cells by Northern and Western blotting,

Results: Ribonuclease protection assays demonstrated connective tissue growth factor mRNA was increased 3-5-fold in **human** fibrotic liver compared with normal, RT-PCR showed this mRNA was increased in carbon-tetrachloride-treated rat liver, Northern analysis showed connective tissue growth factor mRNA was increasingly expressed during progressive activation of cultured rat hepatic stellate cells, Western analysis confirmed that freshly isolated hepatic stellate cells secreted relatively little connective tissue growth factor compared with hepatic stellate cells activated in culture, Hepatic stellate cells stimulated with transforming growth factor-beta 1 showed increased expression of

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Conclusions: Connective tissue growth factor mRNA is consistently upregulated in **human** liver cirrhosis of various aetiologies, supporting a role for this growth factor in hepatic fibrogenesis. Our studies suggest that hepatic stellate cells may be an important source of hepatic connective tissue growth factor in vivo, particularly following stimulation with transforming growth factor-beta.

L12 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS

1999:784118 Document No. 132:31280 sequence and map position and functional expression of **human** connective tissue growth factor-4 for therapeutic and diagnostic applications. Ruben, Steven M.; Young, Paul

E.

(Human Genome Sciences, Inc., USA). PCT Int. Appl. WO 9962927 A1 19991209, 197 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US12150 19990603. PRIORITY: US 1998-88320 19980605.

AB The present invention relates to a novel **human** protein called Connective Tissue Growth Factor-4, and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this **human** protein. The invention further relates to diagnostic and therapeutic methods useful

for diagnosing and treating disorders related to this novel **human** protein. Tissue distribution of **CTGF**-4 polypeptides and chromosomal mapping of this gene are presented. Bacterial, baculovirus and mammalian cell expression of **CTGF**-4 and a purifn. strategy from inclusion bodies is included. **CTGF**-4 fusion proteins are also presented. Antibody prodn. is also relayed. Supernatant prodn. of **CTGF**-4 protein for high-throughput screening assays is described. Activated proteins in the Jaks-STATs pathway bind to gamma activation

site "GAS" elements. Thus, by using GAS elements linked to reporter mols., activators of the Jaks-STATs pathway are identified. High-throughput screening assays for T-cell or myeloid or neuronal or tyrosine kinase or phosphorylation activity is also described. A high-throughput screening assay to identify changes in small mol. concn. and membrane permeability is described. Methods for detg. alterations of the **CTGF**-4 gene are relayed in addn. to methods detecting abnormal **CTGF**-4 protein levels. Gene therapy approaches and **transgenic** animals are used as well. Assays detecting simulation or inhibition of B cell proliferation and differentiation are described. Effect of **CTGF**-4 on the expression of MHC class II, costimulatory and adhesion mols.

and cell differentiation of monocytes and monocyte-derived **human** dendritic cells is explored. The effects of **CTGF**-4 growth/proliferation of vascular endothelium is discussed as well. **CTGF**-4 role in angiogenesis and vasodilation and diabetes and wound healing are also relayed. This protein contains the IGF-binding domain and von Willebrand factor type C repeat domain and sulfated Glycoconjugate binding motif domain and C-terminal dimerization and receptor binding domain.

L12 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS

1999:460440 Document No. 131:101260 Monoclonal antibody against connective tissue growth factor and medicinal uses thereof. Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

AB Disclosed is a **human** monoclonal antibody useful for remedying various diseases caused by **human** connective tissue growth factor (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various monoclonal antibodies having various characteristics

against various mammalian connective tissue growth factors (mCTGFs) useful

for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The **CTGF**-assocd. diseases include cell proliferation-accompanying diseases of or fibrosis of lung, hear, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, **human CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal antibody in rabbits. Similarly, monoclonal anti-hCTGF and mouse **CTGF** antibodies and producing hybridomas were prepd. Prepd. antibodies were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in mice model. Mol. cloning of prepd. **human** monoclonal anti-hCTGF antibody was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prepd. antibodies and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L12 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor.

Takigawa,

Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388 19980904.

AB A medicinal compn. contg. an antibody having a reactivity with **human CTGF** (connective tissue growth factor) has been found out to inhibit the proliferation and migration of vascular

endothelial cells and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic retinopathy, arteriosclerosis, arterial reconstruction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation

or metastasis of tumor, and inflammation in various organs). Thus, recombinant **human CTGF** was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit monoclonal anti-**human CTGF** antibody was prepd. using CEADLEEIK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., **transgenic** mice were used for raising **human** monoclonal anti-**human CTGF** antibodies and hybridomas producing them.

L12 ANSWER 6 OF 7 MEDLINE

1999438098 Document Number: 99438098. PubMed ID: 10506580. Connective tissue growth factor mediates transforming growth factor beta-induced collagen synthesis: down-regulation by cAMP. Duncan M R; Frazier K S; Abramson S; Williams S; Klapper H; Huang X; Grotendorst G R. (Department of Cell Biology and Anatomy, University of Miami School of Medicine, Miami, Florida 33136, USA. ) FASEB JOURNAL, (1999 Oct) 13 (13) 1774-86. Journal code: FAS; 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a cysteine-rich peptide synthesized and secreted by fibroblastic cells after activation with transforming growth factor beta (TGF-beta) that acts as a downstream mediator of TGF-beta-induced fibroblast proliferation. We performed in vitro and in vivo studies to determine whether **CTGF** is also essential for TGF-beta-induced fibroblast collagen synthesis. In vitro studies with normal rat kidney (NRK) fibroblasts demonstrated **CTGF** potently induces collagen synthesis and transfection with an antisense **CTGF** gene blocked TGF-beta stimulated collagen synthesis. Moreover, TGF-beta-induced collagen synthesis in both NRK and **human** foreskin fibroblasts was effectively blocked with specific anti-**CTGF** antibodies and by suppressing TGF-beta-induced **CTGF** gene expression by elevating intracellular cAMP levels with either membrane-permeable 8-Br-cAMP or an adenylyl cyclase activator, cholera toxin (CTX). cAMP also inhibited collagen synthesis induced by **CTGF** itself, in contrast to its previously reported lack of effect on **CTGF**-induced DNA synthesis. In animal assays, CTX injected intradermally in **transgenic** mice suppressed TGF-beta activation of a **human CTGF** promoter/lacZ reporter transgene. Both 8-Br-cAMP and CTX blocked TGF-beta-induced collagen deposition in a wound chamber model of fibrosis in rats. CTX also reduced dermal granulation tissue fibroblast population increases induced by TGF-beta in neonatal mice, but not increases induced by **CTGF** or TGF-beta combined with **CTGF**. Our data indicate that **CTGF** mediates TGF-beta-induced fibroblast collagen synthesis and that in vivo blockade of **CTGF** synthesis or action reduces TGF-beta-induced granulation tissue formation by inhibiting both collagen synthesis and fibroblast accumulation.

L12 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS

1998:341593 Document No. 129:50106 Cloning and expression of cDNA for **human** connective tissue growth factor-3 and clinical use. Ebner, Reinhard; Chopra, Arvind; Ruben, Steven M. (Human Genome Sciences, Inc.,

USA; Ebner, Reinhard; Chopra, Arvind; Ruben, Steven M.). PCT Int. Appl.  
 WO 9821236 A1 19980522, 87 pp. DESIGNATED STATES: W: AM, AU, BG, BR,  
 BY,  
 CA, CN, CZ, EE, FI, GE, HU, IL, JP, KG, KP, KR, KZ, LT, LV, MD, MN, MX,  
 NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, UA, US, UZ, VN, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE,  
 IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO  
 1996-US17856 19961108.  
 AB The cDNA of a novel **human** connective tissue growth factor-3 (  
**CTGF-3**) protein, which is a member of the growth factor  
 superfamily, is isolated and its amino acid sequence deduced. Expression  
 of **CTGF-3** in **transgenic** animal cell lines COS and CHO,  
 and its distribution in **human** tissues are also shown. Also  
 provided are diagnostic and therapeutic methods for detecting and  
 treating  
 connective tissue-related disorders.

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4 FILES SEARCHED...

L16 6 L15 AND CONNECTIVE TISSUE GROWTH FACTOR

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L17 6 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> d l17 1-6 cbib abs

L17 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

2001:197971 Document No.: PREV200100197971. Overexpression of

**connective tissue growth factor**

/hypertrophic chondrocyte-specific gene product 24 decreases bone density

in adult mice and induces dwarfism. Nakanishi, Tohru; Yamaai, Tomoichiro; Asano, Masahiro; Nawachi, Kumiko; Suzuki, Misao; Sugimoto, Tomosada; Takigawa, Masaharu (1). (1) Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Okayama, 700-8525: takigawa@dent.okayama-u.ac.jp Japan. Biochemical and Biophysical Research Communications, (March 2, 2001) Vol. 281, No. 3, pp. 678-681. print.

ISSN:

0006-291X. Language: English. Summary Language: English.

AB **Connective tissue growth factor**

/hypertrophic chondrocyte-specific gene product 24 (CTGF/Hcs24) is a multifunctional growth factor for fibroblasts, chondrocytes, and vascular endothelial cells. In the present study, we established **transgenic** (Tg) mice that over-produce CTGF/Hcs24 under the control of mouse type XI collagen promoter. Tg mice could develop and their embryonic and neonatal growth occurred normally. But they showed dwarfism within a few months of birth. X-ray analysis revealed that their bone density was decreased compared with normal mice. The femurs in the hindlimbs in particular showed an apparent low density. These results indicated that overexpression of CTGF/Hcs24 affects certain steps of endochondral ossification. In addition, the testes were much smaller than normal and fertility was affected in Tg mice, indicating that CTGF/Hcs24 may also regulate the embryonic development of the testis.

L17 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)

2000:356797 The Genuine Article (R) Number: 311EJ. Increased expression of **connective tissue growth factor** in fibrotic human liver and in activated hepatic stellate cells. Williams E J (Reprint); Gaca M D A; Brigstock D R; Arthur M J P; Benyon R C. UNIV SOUTHAMPTON, SOUTHAMPTON GEN HOSP, D LEVEL, S ACAD BLOCK, SOUTHAMPTON

SO16

6YD, HANTS, ENGLAND (Reprint); OHIO STATE UNIV, DEPT SURG, COLUMBUS, OH 43210; OHIO STATE UNIV, DEPT MED BIOCHEM, COLUMBUS, OH 43210; CHILDRENS HOSP, DEPT SURG, COLUMBUS, OH 43205. JOURNAL OF HEPATOLOGY (MAY 2000)

Vol.

32, No. 5, pp. 754-761. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0168-8278. Pub. country: ENGLAND; USA. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

Background/Aims: **Connective tissue growth**

**factor** is a recently described mitogenic protein implicated in a variety of fibrotic disorders, **Connective tissue growth factor** may be a downstream mediator of the pro-fibrotic and mitogenic actions of transforming growth factor-beta, promoting extracellular matrix deposition and fibrogenesis, As transforming growth factor-beta is considered important to the pathogenesis of hepatic fibrosis, we examined the possible contribution

of

**connective tissue growth factor** to this process,

**Methods: Connective tissue growth**

**factor** expression was examined in normal and fibrotic human and rat livers using RT-PCR and ribonuclease protection assays, and in primary

cultures of rat hepatic stellate cells by Northern and Western blotting,

**Results: Ribonuclease protection assays demonstrated connective tissue growth factor** mRNA was increased

3-5-fold in human fibrotic liver compared with normal, RT-PCR showed this mRNA was increased in carbon-tetrachloride-treated rat liver, Northern

analysis showed **connective tissue growth factor** mRNA was increasingly expressed during progressive activation of cultured rat hepatic stellate cells, Western analysis confirmed that freshly isolated hepatic stellate cells secreted relatively

little **connective tissue growth**

**factor** compared with hepatic stellate cells activated in culture, Hepatic stellate cells stimulated with transforming growth factor-beta 1 showed increased expression of **connective tissue growth factor** mRNA and protein,

Conclusions: **Connective tissue growth**

**factor** mRNA is consistently upregulated in human liver cirrhosis of various aetiologies, supporting a role for this growth factor in hepatic fibrogenesis, Our studies suggest that hepatic stellate cells may be an important source of hepatic **connective tissue growth factor** in vivo, particularly following stimulation with transforming growth factor-beta.

L17 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2001 ACS

1999:784118 Document No. 132:31280 sequence and map position and functional expression of human **connective tissue growth**

**factor-4** for therapeutic and diagnostic applications. Ruben, Steven M.; Young, Paul E. (Human Genome Sciences, Inc., USA). PCT Int. Appl. WO 9962927 A1 19991209, 197 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US12150 19990603. PRIORITY: US 1998-88320 19980605.

AB The present invention relates to a novel human protein called

**Connective Tissue Growth Factor-4**,

and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant **methods** for producing this human protein. The invention further relates to

diagnostic

and therapeutic **methods** useful for diagnosing and treating disorders related to this novel human protein. Tissue distribution of CTGF-4 polypeptides and chromosomal mapping of this gene are presented. Bacterial, baculovirus and mammalian cell expression of CTGF-4 and a purifn. strategy from inclusion bodies is included. CTGF-4 fusion proteins are also presented. Antibody prodn. is also relayed. Supernatant prodn. of CTGF-4 protein for high-throughput screening assays is described. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements. Thus, by using GAS elements linked to reporter mols., activators of the Jaks-STATs pathway are identified. High-throughput screening assays for T-cell or myeloid or neuronal or tyrosine kinase or phosphorylation activity is also described. A high-throughput screening assay to identify changes in small mol. concn. and membrane permeability is described. **Methods** for detg. alterations of the CTGF-4 gene are relayed in addn. to **methods** detecting abnormal CTGF-4 protein levels. Gene therapy approaches and **transgenic** animals are used as well. Assays detecting simulation or inhibition of B cell proliferation and differentiation are described. Effect of CTGF-4 on the expression of MHC class II, costimulatory and adhesion mols. and cell differentiation of monocytes and monocyte-derived

human dendritic cells is explored. The effects of CTGF-4 growth/proliferation of vascular endothelium is discussed as well.

CTGF-4

role in angiogenesis and vasodilation and diabetes and wound healing are also relayed. This protein contains the IGF-binding domain and von Willebrand factor type C repeat domain and sulfated Glycoconjugate

binding

motif domain and C-terminal dimerization and receptor binding domain.

L17 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS

1999:613959 Document No. 131:224485 Cloning of cDNA sequence encoding rat heparin-induced CCN-like molecules (HICP) and its therapeutic uses. Castellot, John J., Jr. (Trustees of Tufts College, USA). PCT Int. Appl. WO 9947556 A2 19990923, 108 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US5999 19990318. PRIORITY: US 1998-44273 19980319.

AB Novel HICP polypeptides, proteins, and nucleic acid mols. which play a role in cell proliferation and fibrosis are disclosed. The cDNA was obtained from a rat subtraction cDNA library which was enriched for sequences in fetal calf serum and heparin-treated vascular smooth muscle cells (VSMC) vs. VSMC treated only with FCS. Rat HICP is 250 amino acid residues in length, contg. a 23-residue signal peptide, an insulin-like growth factor-binding protein motif, a von Willebrands C motif, and a thrombospondin motif. In addn. to isolated, full-length HICP proteins, the invention further provides isolated HICP fusion proteins, antigenic peptides and anti-HICP antibodies. Heparin does not upregulate HICP expression in cells unresponsive to the antiproliferative effect of heparin. The invention also provides HICP nucleic acid mols.,

recombinant

expression vectors contg. a nucleic acid mol. of the invention, host cells

into which the expression vectors have been introduced and non-human **transgenic** animals in which a HICP gene has been introduced or disrupted. Diagnostic, screening and therapeutic **methods** utilizing comps. of the invention are also provided.

L17 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

2000:8218 Document No.: PREV200000008218. **Connective tissue growth factor** mediates transforming growth factor beta-induced collagen synthesis: Down-regulation by cAMP. Duncan, Matthew R.; Frazier, Ken S.; Abramson, Susan; Williams, Shawn; Klapper, Helene; Huang, Xinfan; Grotendorst, Gary R. (1). (1) Department of Cell Biology and Anatomy, University of Miami School of Medicine (R-124), 1600 NW 10th Ave., Miami, FL, 33136 USA. FASEB Journal, (Oct., 1999) Vol. 13, No. 13, pp. 1774-1786. ISSN: 0892-6638. Language: English. Summary Language: English.

AB **Connective tissue growth factor**

(CTGF) is a cysteine-rich peptide synthesized and secreted by fibroblastic

cells after activation with transforming growth factor beta (TGF-beta) that acts as a downstream mediator of TGF-beta-induced fibroblast proliferation. We performed in vitro and in vivo studies to determine

whether CTGF is also essential for TGF-beta-induced fibroblast collagen synthesis. In vitro studies with normal rat kidney (NRK) fibroblasts demonstrated CTGF potently induces collagen synthesis and transfection with an antisense CTGF gene blocked TGF-beta stimulated collagen synthesis. Moreover, TGF-beta-induced collagen synthesis in both NRK and human foreskin fibroblasts was effectively blocked with specific anti-CTGF antibodies and by suppressing TGF-beta-induced CTGF gene expression by elevating intracellular cAMP levels with either membrane-permeable 8-Br-cAMP or an adenylyl cyclase activator, cholera toxin (CTX). cAMP also inhibited collagen synthesis induced by CTGF itself, in contrast to its previously reported lack of effect on CTGF-induced DNA synthesis. In animal assays, CTX injected intradermally in **transgenic** mice suppressed TGF-beta activation of a human CTGF promoter/lacZ reporter transgene. Both 8-Br-cAMP and CTX blocked TGF-beta-induced collagen deposition in a wound chamber model of fibrosis in rats. CTX also reduced dermal granulation tissue fibroblast population increases induced by TGF-beta in neonatal mice, but not increases induced by CTGF or TGF-beta combined with CTGF. Our data indicate that CTGF mediates TGF-beta-induced fibroblast collagen synthesis and that in vivo blockade of CTGF synthesis or action reduces TGF-beta-induced granulation tissue formation by inhibiting both collagen synthesis and fibroblast accumulation.

L17 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS  
 1998:341593 Document No. 129:50106 Cloning and expression of cDNA for human **connective tissue growth factor-3** and clinical use. Ebner, Reinhard; Chopra, Arvind; Ruben, Steven M. (Human Genome Sciences, Inc., USA; Ebner, Reinhard; Chopra, Arvind; Ruben, Steven M.). PCT Int. Appl. WO 9821236 A1 19980522, 87 pp. DESIGNATED STATES: W: AM, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, JP, KG, KP, KR, KZ, LT, LV, MD, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US17856 19961108.

AB The cDNA of a novel human **connective tissue growth factor-3** (CTGF-3) protein, which is a member of the growth factor superfamily, is isolated and its amino acid sequence deduced. Expression of CTGF-3 in **transgenic** animal cell lines COS and CHO, and its distribution in human tissues are also shown. Also provided are diagnostic and therapeutic **methods** for detecting and treating connective tissue-related disorders.

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L18 9771 (TAMATANI T?/AU OR TEZUKA K?/AU OR SAKAMOTO S?/AU OR TAKIGAWA M?/AU)

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L21 ANSWER 1 OF 34 MEDLINE

2001216125 Document Number: 21134299. PubMed ID: 11237711.

Overexpression

of **connective tissue growth factor**

/hypertrophic chondrocyte-specific gene product 24 decreases bone density in adult mice and induces dwarfism. Nakanishi T; Yamaai T; Asano M; Nawachi K; Suzuki M; Sugimoto T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Okayama, 700-8525, Japan. ) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Mar 2) 281 (3) 678-81. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB **Connective tissue growth factor**

/hypertrophic chondrocyte-specific gene product 24 (CTGF/Hcs24) is a multifunctional growth factor for fibroblasts, chondrocytes, and vascular endothelial cells. In the present study, we established transgenic (Tg) mice that overproduce CTGF/Hcs24 under the control of mouse type XI collagen promoter. Tg mice could develop and their embryonic and neonatal growth occurred normally. But they showed dwarfism within a few months of birth. X-ray analysis revealed that their bone density was decreased compared with normal mice. The femurs in the hindlimbs in particular showed an apparent low density. These results indicated that overexpression of CTGF/Hcs24 affects certain steps of endochondral ossification. In addition, the testes were much smaller than normal and fertility was affected in Tg mice, indicating that CTGF/Hcs24 may also regulate the embryonic development of the testis. Copyright 2001 Academic Press.

L21 ANSWER 2 OF 34 MEDLINE

2001262529 Document Number: 21230052. PubMed ID: 11332533. Mechanical

stimulation induces CTGF expression in rat osteocytes. Yamashiro T; Fukunaga T; Kobashi N; Kamioka H; Nakanishi T; **Takigawa M;** Takano-Yamamoto T. (Department of Orthodontics, Okayama University Dental School, Japan. ) JOURNAL OF DENTAL RESEARCH, (2001 Feb) 80 (2) 461-5. Journal code: HYV; 0354343. ISSN: 0022-0345. Pub. country: United States. Language: English.

AB **Connective tissue growth factor**

(CTGF), which is encoded by an immediate early gene and a member of the CCN family, has been shown to be expressed in osteoblasts, fibroblasts, and chondrocytes. Although CTGF is expressed in bone and cartilage tissues, we tested the hypothesis that CTGF is regulated in mechanotransduction. In the alveolar bone during experimental tooth movement, CTGF mRNA was expressed in osteoblasts and in osteocytes localized around the periodontal ligament under control conditions. Interestingly, 12 hrs after the start of experimental tooth movement, the expression of CTGF mRNA in osteocytes and osteoblasts became more intense

around the periodontal ligament, and the intense expression of CTGF extended to osteocytes situated deep in alveolar bone matrix apart from periodontal ligament in both tension and compression sides. Our present findings indicate that CTGF could play a role in regulation of osteocyte function during the mechanical stimulation of bone.

L21 ANSWER 3 OF 34 MEDLINE

2000479434 Document Number: 20484756. PubMed ID: 11032028.

Identification

of an RNA element that confers post-transcriptional repression of **connective tissue growth factor** /hypertrophic chondrocyte specific 24 (ctgf/hcs24) gene: similarities to retroviral RNA-protein interactions. Kubota S; Kondo S; Eguchi T; Hattori T; Nakanishi T; Pomerantz R J; **Takigawa M**. (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Japan. ) ONCOGENE, (2000 Sep 28) 19 (41) 4773-86. Journal code: ONC. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language:

English.

AB The repressive effect of the 3'-untranslated region (3'-UTR) in human **connective tissue growth factor**/hypertrophic chondrocyte specific 24 (ctgf/hcs24) mRNA on gene expression had been demonstrated in our previous study. Here, we identified a

minimal

RNA element in the 3'-UTR, which acts as a cis-acting element of structure-anchored repression (CAESAR). Deletion analyses of the 3'-UTR led us to minimize the element of 84 bases at the junction of the coding region and the 3'-UTR. The minimized RNA segment is predicted, and actually capable of forming a stable secondary structure in vitro. Mutational analyses disclosed a significant relationship between the predicted structure and repressive effect. The utility of CAESAR as a post-transcriptional regulatory element was represented by the fact that steady-state mRNA levels were not affected by CAESAR linked in cis, while protein levels from such a chimeric gene were markedly reduced. Of note, the CAESAR sequence exerted no effect, when it was placed upstream of the promoter. Finally, RNA gel electromobility-shift analyses demonstrated a nuclear factor that interacts with the folded CAESAR. Taken together, it was uncovered that CAESAR of ctgf is a novel post-transcriptional structured RNA regulatory element, probably acting through direct interactions with a nuclear factor as observed in retroviral RNA elements with certain proteins.

L21 ANSWER 4 OF 34 MEDLINE

2000467068 Document Number: 20469237. PubMed ID: 11013359. Expression of

**connective tissue growth factor** in cartilaginous tumors. Shakunaga T; Ozaki T; Ohara N; Asaumi K; Doi T; Nishida K; Kawai A; Nakanishi T; **Takigawa M**; Inoue H. (Department of Orthopaedic Surgery, Faculty of Medicine, Okayama University Medical School, Okayama, Japan. ) CANCER, (2000 Oct 1) 89 (7) 1466-73. Journal code: CLZ; 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: **Connective tissue growth factor** (CTGF) predominantly is expressed in hypertrophic chondrocytes and its specific receptors are demonstrated on chondrocytic cells. Therefore, CTGF may be involved in the proliferation and/or differentiation of cartilage cells. In the current study, CTGF expression was examined both in chondrosarcoma and enchondroma to clarify the relation between the expression of CTGF and the grade of malignancy. METHODS: The expression of CTGF and proliferating cell nuclear antigen

(PCNA) were analyzed immunohistochemically in 34 cartilaginous tumor specimens. Eighteen tumors were determined to be chondrosarcoma including 8 Grade 1 tumors, 6 Grade 2 tumors, and 4 Grade 3 tumors. The percentage of CTGF positive and PCNA positive cells was quantified using at least 500 cells. RESULTS: CTGF was expressed in 70.1% of enchondroma cells, 84.0% of Grade 1 chondrosarcoma cells, 53.7% of Grade 2 tumor cells, and 26.8% of Grade 3 tumor cells ( $\rho = -0.501$ ;  $P = 0.0053$ ). In chondrosarcoma cases, CTGF expression was correlated closely with tumor grade ( $\rho = -0.920$ ;  $P = 0.0001$ ). There was a strong correlation between PCNA expression and tumor grade ( $\rho = 0.907$ ;  $P < 0.0001$ ) and a strong negative correlation between CTGF and PCNA expression ( $\rho = -0.493$ ;  $P = 0.0061$ ). In chondrosarcoma cases, patients with high expression of CTGF ( $\geq 30\%$ ) showed higher overall survival compared with those with low expression ( $< 30\%$ ) ( $P = 0.004$ ). CONCLUSIONS: The current study revealed a correlation between the histologic grade of chondrosarcoma and prognosis, and the concomitant association between CTGF immunostaining and tumor grade and prognosis. Therefore, immunohistochemical staining with CTGF is a useful procedure for assessing the tumor grade and clinical course in patients with chondrosarcoma.

L21 ANSWER 5 OF 34 SCISEARCH COPYRIGHT 2001 ISI (R)  
 2001:17464 The Genuine Article (R) Number: 359PZ. Expression of **connective tissue growth factor** in the liver of patients with chronic hepatitis C and idiopathic portal hypertension.. Morikawa H (Reprint); Nishiguchi S; Shiomi S; Seki S; Kaneda K; Nakanishi T; **Takigawa M.** Okayama Univ, Okayama, Japan; Osaka City Univ, Sch Med, Osaka 558, Japan. HEPATOLOGY (OCT 2000) Vol. 32, No. 4, Part 2, pp. 505A-505A. MA 1384. Publisher: W B SAUNDERS CO. INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. ISSN: 0270-9139. Pub. country: Japan. Language: English.

L21 ANSWER 6 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS  
 2000:413154 Document No.: PREV200000413154. A novel RNA element that confers post-transcriptional repression of human **connective tissue growth factor**/hypertrophic chondrocyte specific 24 (ctgf/hcs24) gene. Kubota, S. (1); Kondo, S. (1); Eguchi, T. (1); Hattori, T. (1); Nakanishi, T. (1); Pomerantz, R. J.; **Takigawa, M. (1).** (1) Biochemistry, Okayama University Dental School, Okayama Japan. Journal of Bone and Mineral Research, (September, 2000) Vol. 15, No. Suppl. 1, pp. S340. print. Meeting Info.: Twenty-Second Annual Meeting of the American Society for Bone and Mineral Research Toronto, Ontario, Canada September 22-26, 2000 American Society for Bone and Mineral Research. ISSN: 0884-0431. Language: English. Summary Language: English.

L21 ANSWER 7 OF 34 MEDLINE  
 2000080284 Document Number: 20080284. PubMed ID: 10614647. Effects of CTGF/Hcs24, a product of a hypertrophic chondrocyte-specific gene, on the proliferation and differentiation of chondrocytes in culture. Nakanishi T; Nishida T; Shimo T; Kobayashi K; Kubo T; **Tamatani T; Tezuka K; Takigawa M.** (Department of Biochemistry and Molecular Dentistry, Biodental Research Center, Okayama University Dental School, Japan. ) ENDOCRINOLOGY, (2000 Jan) 141 (1) 264-73. Journal code: EGZ;

0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.  
AB Recently, we cloned a messenger RNA (mRNA) predominantly expressed in  
chondrocytes from a human chondrosarcoma-derived chondrocytic cell line,  
HCS-2/8, by differential display PCR and found that its gene, named  
hcs24,

was identical with that of **connective tissue  
growth factor** (CTGF). Here we investigated CTGF/Hcs24  
function in the chondrocytic cell line HCS-2/8 and rabbit growth  
cartilage

(RGC) cells. HCS-2/8 cells transfected with recombinant adenoviruses that  
generate CTGF/Hcs24 sense RNA (mRNA) proliferated more rapidly than  
HCS-2/8 cells transfected with control adenoviruses. HCS-2/8 cells  
transfected with recombinant adenoviruses that generate CTGF/Hcs24 sense  
RNA expressed more mRNA of aggrecan and type X collagen than the control  
cells. To elucidate the direct action of CTGF/Hcs24 on the cells, we  
transfected HeLa cells with CTGF/Hcs24 expression vectors, obtained  
stable

transfectants, and purified recombinant CTGF/Hcs24 protein from  
conditioned medium of the transfectants. The recombinant CTGF/Hcs24  
effectively promoted the proliferation of HCS-2/8 cells and RGC cells in

a  
dose-dependent manner and also dose dependently increased proteoglycan  
synthesis in these cells. In addition, these stimulatory effects of  
CTGF/Hcs24 were neutralized by the addition of anti-CTGF antibodies.  
Furthermore, the recombinant CTGF/Hcs24 effectively increased alkaline  
phosphatase activity in RGC cells in culture. Moreover, RT-PCR analysis  
revealed that the recombinant CTGF/Hcs24 stimulated gene expression of  
aggrecan and collagen types II and X in RGC cells in culture. These  
results indicate that CTGF/Hcs24 directly promotes the proliferation and  
differentiation of chondrocytes.

L21 ANSWER 8 OF 34 MEDLINE

2000396788 Document Number: 20327711. PubMed ID: 10867644. Effects of  
CTGF/Hcs24, a hypertrophic chondrocyte-specific gene product, on the  
proliferation and differentiation of osteoblastic cells in vitro. Nishida  
T; Nakanishi T; Asano M; Shimo T; **Takigawa M.** (Department of  
Biochemistry and Molecular Dentistry, Okayama University Dental School,  
Okayama, Japan. ) JOURNAL OF CELLULAR PHYSIOLOGY, (2000 Aug) 184 (2)  
197-206. Journal code: HNB; 0050222. ISSN: 0021-9541. Pub. country:  
United States. Language: English.

AB **Connective tissue growth factor**

/hypertrophic chondrocyte-specific gene product Hcs24 (CTGF/Hcs24)  
promotes the proliferation and differentiation of chondrocytes and  
endothelial cells which are involved in endochondral ossification (Shimo  
et al., 1998, J Biochem 124:130-140; Shimo et al., 1999, J Biochem  
126:137-145; Nakanishi et al., 2000, Endocrinology 141:264-273). To  
further clarify the role of CTGF/Hcs24 in endochondral ossification, here  
we investigated the effects of CTGF/Hcs24 on the proliferation and  
differentiation of osteoblastic cell lines in vitro. A binding study

using  
(125)I-labeled recombinant CTGF/Hcs24 (rCTGF/Hcs24) disclosed two classes  
of specific binding sites on a human osteosarcoma cell line, Saos-2. The  
apparent dissociation constant (Kd) value of each binding site was 17.2  
and 391 nM, respectively. A cross-linking study revealed the formation of  
(125)I-rCTGF/Hcs24-receptor complex with an apparent molecular weight of  
280 kDa. The intensity of (125)I-rCTGF/Hcs24-receptor complex decreased

on  
the addition of increasing concentrations of unlabeled rCTGF/Hcs24, but

not platelet-derived growth factor-BB homodimer or basic fibroblast growth factor. These findings suggest that osteoblastic cells have specific receptor molecules for CTGF/Hcs24. rCTGF/Hcs24 promoted the proliferation of Saos-2 cells and a mouse osteoblast cell line MC3T3-E1 in a dose- and time-dependent manner. rCTGF/Hcs24 also increased mRNA expression of type I collagen, alkaline phosphatase, osteopontin, and osteocalcin in both Saos-2 cells and MC3T3-E1 cells. Moreover, rCTGF/Hcs24 increased alkaline phosphatase activity in both cells. It also stimulated collagen synthesis in MC3T3-E1 cells. Furthermore, rCTGF/Hcs24 stimulated the matrix mineralization on MC3T3-E1 cells and its stimulatory effect was comparable to that of bone morphogenetic protein-2. These findings indicate that CTGF/Hcs24 is a novel, potent stimulator for the proliferation and differentiation of osteoblasts in addition to chondrocytes and endothelial cells. Because of these functions, we are re-defining CTGF/Hcs24 as a major factor to promote endochondral ossification to be called "ecogenin: endochondral ossification genetic factor." Copyright 2000 Wiley-Liss, Inc.

L21 ANSWER 9 OF 34 MEDLINE  
 2000112557 Document Number: 20112557. PubMed ID: 10648031. Serum levels of **connective tissue growth factor** are elevated in patients with systemic sclerosis: association with extent of skin sclerosis and severity of pulmonary fibrosis. Sato S; Nagaoka T; Hasegawa M; **Tamatani T**; Nakanishi T; **Takigawa M**; Takehara K. (Department of Dermatology, Kanazawa University School of Medicine, Ishikawa, Japan.. s-sato@med.kanazawa-u.ac.jp) . JOURNAL OF RHEUMATOLOGY, (2000 Jan) 27 (1) 149-54. Journal code: JWX; 7501984.  
 ISSN: 0315-162X. Pub. country: Canada. Language: English.  
 AB OBJECTIVE: To determine the serum levels and clinical correlation of **connective tissue growth factors** (CTGF) in patients with systemic sclerosis (SSc). METHODS: Serum samples from patients with limited cutaneous SSc (lSSc, n = 32), diffuse cutaneous SSc (dSSc, n = 28), systemic lupus erythematosus (SLE, n = 30), polymyositis/dermatomyositis (PM/DM, n = 20), and healthy control subjects (n = 30) were examined by ELISA for detection of CTGF. RESULTS: Serum CTGF levels in patients with SSc were significantly higher than those in patients with SLE or PM/DM, and in controls. CTGF levels in patients with dSSc were significantly higher than those in patients with lSSc. As for clinical correlation of CTGF, SSc patients with elevated CTGF had pulmonary fibrosis, decreased DLCO, and decreased vital capacity more frequently than those with normal CTGF levels. Further, DLCO and vital capacity were inversely and directly correlated with serum CTGF levels in patients with SSc. The dSSc patients with disease duration of 1-3 years had significantly elevated levels of CTGF compared with dSSc patients with duration < 1 year or more than 3 years. CONCLUSION: Serum CTGF levels were increased in patients with SSc, and correlated with the extent of skin sclerosis and the severity of pulmonary fibrosis. In addition, it appears that production of CTGF is involved in the development or maintenance of fibrosis rather than in initiation of fibrosis in SSc. These data suggest

that CTGF plays a critical role in the development of fibrosis in SSC.

L21 ANSWER 10 OF 34 MEDLINE

2001069501 Document Number: 20525415. PubMed ID: 11071863.

Characterization of a mouse ctgf 3'-UTR segment that mediates repressive regulation of gene expression. Kondo S; Kubota S; Eguchi T; Hattori T; Nakanishi T; Sugahara T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, 2-5-1 Shikata-cho, Okayama 700-8525, Japan. ) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Nov 11) 278 (1) 119-24. Journal code:

9Y8.

ISSN: 0006-291X. Pub. country: United States. Language: English.

AB We isolated a small segment of the 3'-untranslated region (3'-UTR) in the mouse **connective tissue growth**

**factor** (ctgf/fisp12) gene and evaluated its functionality.

Comparison of the nucleotide sequences of human and mouse ctgf 3'-UTRs revealed a conserved small segment of 91 bases. The corresponding

segments

of the 3'-UTRs shared as much as 82.4% homology, whereas the overall homology between the 3'-UTRs was 71.8%. To study the functionality of the conserved segment, the corresponding region of mouse ctgf cDNA was amplified from NIH3T3 cells. When it was fused downstream of a marker gene, it showed remarkable repressive effects on gene expression. The repressive effect of the sense form was more prominent than that of the antisense form. Computer analyses of these sequence predicted stable secondary structures, suggesting that they act at the RNA level. The predicted structures of the sense and antisense forms appeared to be slightly different, which is consistent with the difference in repressive function. These findings defined the conserved small element in the mouse ctgf gene as a potent negative regulator of gene expression, which may

act

at a posttranscriptional level.

Copyright 2000 Academic Press.

L21 ANSWER 11 OF 34 MEDLINE

2000291078 Document Number: 20291078. PubMed ID: 10828451. Novel

intracellular effects of human **connective tissue**

**growth factor** expressed in Cos-7 cells. Kubota S;

Hattori T; Shimo T; Nakanishi T; **Takigawa M.** (Department of

Biochemistry and Molecular Dentistry, Okayama University Dental School, 2-5-1 Shikata-cho, Okayama 700-8525, Japan. ) FEBS LETTERS, (2000 May 26) 474 (1) 58-62. Journal code: EUH; 0155157. ISSN: 0014-5793. Pub.

country:

Netherlands. Language: English.

AB To clarify the multiple functionality of **connective tissue growth factor** (CTGF), we examined the

effects of nascent CTGF within the cell by transient expression. In Cos-7 cells, expression of human CTGF induced an altered cell morphology. It

was

associated with an increased cellular DNA content and loose attachment, indicating the cells were in G2/M phase. Overexpression of CTGF did not induce cell growth, whereas recombinant CTGF efficiently stimulated the proliferation extracellularly. These results indicate that intracellular CTGF may act as an antimitotic agent, thus it should also be noted that nascent CTGF was found to accumulate around the central mitotic

machinery.

L21 ANSWER 12 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS

2000:221208 Document No.: PREV200000221208. Roles of Hcs24/CTGF in the occurrence and development of ossification of posterior longitudinal ligament. Yamamoto, Yuji (1); Furukawa, Ken-Ichi; Ueyama, Kazumasa (1); Motomura, Shigeru; Nakanishi, Tohru; **Takigawa, Masaharu**; Harata, Seiko (1). (1) Dep. of Orthop. Surg., Hirosaki Univ. School of Med., Hirosaki, 036-8562 Japan. Japanese Journal of Pharmacology, (2000) Vol. 82, No. Suppl. 1, pp. 46P. Meeting Info.: 73rd Annual Meeting of the Japanese Pharmacological Society. Yokohama, Japan March 23-25, 2000 ISSN: 0021-5198. Language: English. Summary Language: English.

L21 ANSWER 13 OF 34 SCISEARCH COPYRIGHT 2001 ISI (R)

2000:885723 The Genuine Article (R) Number: 346YJ. A novel RNA element that confers post-transcriptional repression of human **connective tissue growth factor**/hypertrophic chondrocyte specific 24 (ctgf/hcs24) gene.. Kubota S (Reprint); Kondo S; Eguchi T; Hattori T; Nakanishi T; Pomerantz R J; **Takigawa M.** OKAYAMA UNIV, SCH DENT, OKAYAMA 700, JAPAN; THOMAS JEFFERSON UNIV, PHILADELPHIA, PA. JOURNAL OF BONE AND MINERAL RESEARCH (SEP 2000) Vol. 15, Supp. [1], pp. SU035-SU035. Publisher: AMER SOC BONE & MINERAL RES. 2025 M ST, N W, STE 800, WASHINGTON, DC 20036-3309. ISSN: 0884-0431. Pub. country: JAPAN; USA.

Language: English.

L21 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2001 ACS

2000:681227 Document No. 134:554 Physiological roles of **connective tissue growth factor** (CTGF / Hcs24): Promotion of endochondral ossification, angiogenesis and tissue remodeling. **Takigawa, Masaharu** (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Okayama, 700, Japan). Int. Congr. Ser., 1198(Tissue Engineering for Therapeutic Use 4), 1-13 (English) 2000. CODEN: EXMDA4. ISSN: 0531-5131. Publisher: Elsevier Science B.V..

AB A review with 44 refs. A hypertrophic chondrocyte specific gene (hcs24) isolated from a human chondrocytic cell line HCS-2/8 was identical to that

of **connective tissue growth factor**

(CTGF). The gene expression of CTGF/Hcs24 was maximal in hypertrophic chondrocytes during the development of embryonic and young animals, suggesting a major physiol. role for this factor in endochondral ossification. In fact, recombinant CTGF protein (rCTGF/Hcs24) promoted the proliferation, maturation and hypertrophy of cultured chondrocytes. Moreover, rCTGF/Hcs24 promoted the adhesion, proliferation and migration of vascular endothelial cells, and induced tube formation by the cells

and

strong angiogenesis in vivo, indicating that CTGF/Hcs24 is a novel, potent

angiogenesis factor as well. Furthermore, rCTGF/Hcs24 stimulated the proliferation and differentiation of cultured osteoblastic cells. These findings suggest that CTGF/Hcs24 produced by hypertrophic chondrocytes promotes the whole process of endochondral ossification by acting on the three types of cells as a paracrine factor. Because of these functions, we are redefining CTGF as a major factor to promote endochondral ossification, to be called "ecogenin". The finding that CTGF/Hcs24 was expressed in periosteal cells and hypertrophic chondrocytes during the healing of exptl. bone fracture also suggests its importance in endochondral ossification and a possible role in skeletal repair. The factor may have applications in tissue engineering for the repair of cartilage and bone. The strong angiogenic activity of this factor also

may provide for tissue engineering for the vascular system.

L21 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2001 ACS

1999:460440 Document No. 131:101260 Monoclonal antibody against

**connective tissue growth factor** and

medicinal uses thereof. **Tamatani, Takuya; Tezuka,**

**Katsunari; Sakamoto, Shinji; Takigawa, Masaharu**

(Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp.

DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

AB Disclosed is a human monoclonal antibody useful for remedying various diseases caused by human **connective tissue growth factor** (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various monoclonal antibodies

having various characteristics against various mammalian

**connective tissue growth factors**

(mCTGFs) useful for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The

CTGF-assocd.

diseases include cell proliferation-accompanying diseases of or fibrosis of lung, heart, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, human CTGF (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal antibody in rabbits. Similarly, monoclonal anti-hCTGF and mouse CTGF antibodies and producing hybridomas were prepd. Prepd. antibodies were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian CTGFs and treatment of tissue fibrosis in mice model. Mol. cloning of prepd. human monoclonal anti-hCTGF antibody was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prepd. antibodies and fragments was used for detecting serum or synovial CTGF in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L21 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2001 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor.

**Takigawa, Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi** (Japan

Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp.

DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH,

CN,

CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388

19980904.

AB A medicinal compn. contg. an antibody having a reactivity with human CTGF (**connective tissue growth factor**) has been found out to inhibit the proliferation and migration of vascular endothelial cells and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic retinopathy, arteriosclerosis, arterial reconstruction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation or metastasis of tumor, and inflammation in various organs). Thus, recombinant human CTGF was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit monoclonal anti-human CTGF antibody was prepd. using CEADLEEIK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., transgenic mice were used for raising human monoclonal anti-human CTGF antibodies and hybridomas producing them.

L21 ANSWER 17 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS

1999:432336 Document No.: PREV199900432336. A cis-acting repressive element in

the 3'-untranslated region of the CTGF gene. Kubota, S. (1); Hattori, T. (1); Eguchi, T. (1); Kondo, S. (1); Nakanishi, T. (1); **Takigawa, M.**

(1). (1) Department of Biochemistry, Okayama University Dental School, Okayama Japan. Journal of Bone and Mineral Research, (Sept., 1999)

Vol. 14, No. SUPPL. 1, pp. S436. Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999 American Society for Bone and Mineral Research. ISSN: 0884-0431. Language: English.

L21 ANSWER 18 OF 34 MEDLINE

1999361400 Document Number: 99361400. PubMed ID: 10432835. Physiological function of **connective tissue growth factor** (CTGF/Hcs24)--its roles in the process of endochondral ossification. Nakanishi T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School. ) SEIKAGAKU. JOURNAL OF JAPANESE BIOCHEMICAL SOCIETY, (1999 Jun) 71 (6) 429-32. Ref: 15. Journal code: ILZ; 0413564. ISSN: 0037-1017. Pub. country: Japan. Language: Japanese.

L21 ANSWER 19 OF 34 MEDLINE

1999388085 Document Number: 99388085. PubMed ID: 10457363. Role and interaction of **connective tissue growth factor** with transforming growth factor-beta in persistent fibrosis: A mouse fibrosis model. Mori T; Kawara S; Shinozaki M; Hayashi N; Kakinuma T; Igarashi A; **Takigawa M**; Nakanishi T; Takehara K. (Department of Dermatology, Kanazawa University School of Medicine, Kanazawa, Ishikawa, Japan. ) JOURNAL OF CELLULAR PHYSIOLOGY, (1999 Oct) 181 (1) 153-9. Journal code: HNB; 0050222. ISSN: 0021-9541. Pub. country:

United States. Language: English.

AB Skin fibrotic disorders are understood to develop under the influence of some growth factors, such as transforming growth factor-beta (TGF-beta), basic fibroblast growth factor (bFGF), or **connective**

**tissue growth factor** (CTGF). To establish an appropriate animal model of skin fibrosis by exogenous application of growth factors, we investigated the in vivo effects of growth factors by injecting TGF-beta, CTGF, and bFGF into the subcutaneous tissue of newborn mice. A single application of TGF-beta or bFGF resulted in the formation of transient granulated tissue that disappeared despite 7 days of consecutive injections. A single CTGF injection also caused slight granulation. However, injecting TGF-beta plus CTGF produced long-term fibrotic tissue, which persisted for at least 14 days. Also, fibrotic tissue was observed when CTGF was injected from 4 to 7 days after TGF-beta injections for the first 1-3 days. In situ hybridization analysis revealed the expression of CTGF mRNA in the fibroblasts at least in a few fibrotic conditions. These findings suggest that either CTGF mRNA or an application of exogenous CTGF protein is required for the development of persistent fibrosis. From our study, it appears that interaction of several growth factors is required for persistent fibrotic tissue formation, with TGF-beta causing the induction and CTGF needed for maintenance of skin fibrosis. The animal model on skin fibrosis by exogenous application of growth factors developed in this study may prove useful for future studies on fibrotic disorders.

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L21 ANSWER 20 OF 34 MEDLINE

1999337606 Document Number: 99337606. PubMed ID: 10407104.

Immunohistochemical localization of **connective tissue growth factor** in the rat central nervous system. Kondo Y; Nakanishi T; **Takigawa M**; Ogawa N. (Department of Neuroscience, Institute of Molecular and Cellular Medicine, Okayama University Medical School, 2-5-1 Shikatacho, Okayama 700-8558, Japan. ) BRAIN RESEARCH, (1999 Jul 10) 834 (1-2) 146-51. Journal code: B5L; 0045503. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.

AB **Connective tissue growth factor**

(CTGF) is an immediate early growth-responsive gene but its distribution and significance in the central nervous system (CNS) are unknown. We investigated the distribution of CTGF-like immunoreactivity (CTGF-IR) in the rat CNS using a specific antiserum against CTGF oligopeptide. The majority of CTGF-IR was observed in astrocytes. Ependymal cells lining the wall of the cerebral ventricle and tanocytes lining the central canal of the spinal cord showed the strongest CTGF-IR, while there was a diffuse but weak signal in the gray matter of the spinal cord. CTGF-IR was also detected in the cytoplasm of a subpopulation of pyramidal neurons in the cerebral cortex. Our results showed that CTGF-IR is widely distributed in the CNS at both regional and cellular levels, suggesting a complex functional role in the CNS.

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L21 ANSWER 21 OF 34 MEDLINE

1999321851 Document Number: 99321851. PubMed ID: 10393331.

**Connective tissue growth factor**

induces the proliferation, migration, and tube formation of vascular endothelial cells in vitro, and angiogenesis in vivo. Shimo T; Nakanishi T; Nishida T; Asano M; Kanyama M; Kuboki T; **Tamatani T**;

**Tezuka K; Takemura M; Matsumura T; Takigawa M.**

(Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Okayama, 700-8525, Japan. ) JOURNAL OF BIOCHEMISTRY, (1999 Jul) 126 (1) 137-45. Journal code: HIF; 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB **Connective tissue growth factor**

(CTGF) is a novel cysteine-rich, secreted protein. Recently, we found that

inhibition of the endogenous expression of CTGF by its antisense oligonucleotide and antisense RNA suppresses the proliferation and migration of vascular endothelial cells. In the present study, the following observations demonstrated the angiogenic function of CTGF in vitro and in vivo: (i) purified recombinant CTGF (rCTGF) promoted the adhesion, proliferation and migration of vascular endothelial cells in a dose-dependent manner under serum-free conditions, and these effects were inhibited by anti-CTGF antibodies; (ii) rCTGF markedly induced the tube formation of vascular endothelial cells, and this effect was stronger

than

that of basic fibroblast growth factor or vascular endothelial growth factor; (iii) application of rCTGF to the chicken chorioallantoic

membrane

resulted in a gross angiogenic response, and this effect was also inhibited by anti-CTGF antibodies. (iv) rCTGF injected with collagen gel into the backs of mice induced strong angiogenesis in vivo. These

findings

indicate that CTGF is a novel, potent angiogenesis factor which functions in multi-stages in this process.

L21 ANSWER 22 OF 34 MEDLINE

1999277565 Document Number: 99277565. PubMed ID: 10350062. Involvement of

cis-acting repressive element(s) in the 3'-untranslated region of human **connective tissue growth factor**

gene. Kubota S; Hattori T; Nakanishi T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School,

Japan. ) FEBS LETTERS, (1999 Apr 30) 450 (1-2) 84-8. Journal code: EUH; 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB To analyze the regulatory mechanism of **connective tissue growth factor** expression, the 3'-untranslated region

(3'-UTR) of CTGF cDNA was amplified from HeLa cell RNA. Direct nucleotide sequencing revealed a single major population in the amplicon, which was nearly identical to other sequences. Subsequently, the effect of the 3'-UTR on gene expression was evaluated. When it was fused downstream of

a

firefly luciferase gene, the 3'-UTR strongly repressed luciferase gene expression. Interestingly, the repressive effect of the antisense 3'-UTR appeared to be more prominent than that of the sense one. Together with the fact that several consensus sequences for regulatory elements are found in it, these results suggest the involvement of multiple sets of regulatory elements in the CTGF 3'-UTR.

L21 ANSWER 23 OF 34 SCISEARCH COPYRIGHT 2001 ISI (R)

1999:858604 The Genuine Article (R) Number: 230DT. Expression of **connective tissue growth factor**

(CTGF) in pulmonary fibrosis. Pan L H (Reprint); Yamauchi K; Yoshida K; Nakanishi T; **Takigawa M**; Uzuki M; Mouri T; Ito H; Shikanai T; Inoue H; Sawai T. IWATE MED UNIV, SCH MED, DEPT INTERNAL MED 3, MORIOKA,

IWATE 020, JAPAN; IWATE MED UNIV, SCH MED, DEPT PATHOL 1, MORIOKA, IWATE 020, JAPAN. AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE (MAR 1999) Vol. 159, No. 3, Supp. [S], pp. A68-A68. Publisher: AMER LUNG ASSOC. 1740 BROADWAY, NEW YORK, NY 10019. ISSN: 1073-449X. Pub. country: JAPAN. Language: English.

L21 ANSWER 24 OF 34 MEDLINE

1999122785 Document Number: 99122785. PubMed ID: 9925376. Increased expression of **connective tissue growth**

**factor** in the infarct zone of experimentally induced myocardial infarction in rats. Ohnishi H; Oka T; Kusachi S; Nakanishi T; Takeda K; Nakahama M; Doi M; Murakami T; Ninomiya Y; **Takigawa M**; Tsuji T. (First Department of Internal Medicine, Okayama University Medical

School,

Japan. ) JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, (1998 Nov) 30 (11) 2411-22. Journal code: J72; 0262322. ISSN: 0022-2828. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Connective tissue growth factor**

(CTGF), a 36- to 38-kDa peptide, is selectively induced by transforming growth factor-beta and has been suggested to contribute to tissue repair. To test the hypothesis that CTGF is expressed in myocardial infarct

tissue

following acute myocardial infarction (AMI), we examined CTGF expression after AMI was experimentally induced in rats. Myocardial infarction was induced by left coronary artery ligation in male Sprague-Dawley rats. Northern blotting demonstrated that the CTGF mRNA expression on days 2, 7 and 14 was increased by 6-, 23- and 8-fold, respectively, compared to

that

in the pre-ligation hearts. In situ hybridization revealed CTGF mRNA signals on day 2 in myocytes in the infarct marginal zone and spindle-shaped mesenchymal cells (presumably myofibroblasts and fibroblasts) located between surviving myocytes in the infarct peripheral zone. On day 7, the signals were observed in the inner lesion of the infarct around infarct granulation tissue. Western blotting demonstrated that the CTGF protein expression on days 2, 7 and 14 was increased compared to the pre-ligation hearts. Immunopositive staining for CTGF was observed in the inner lesion of the infarct tissue on day 7. In conclusion, the findings demonstrated the increased expression of CTGF in the infarct tissue. Myocytes in the infarct marginal zone and spindle-shaped mesenchymal cells (presumably myofibroblasts and fibroblasts) were the cells responsible for CTGF production.

L21 ANSWER 25 OF 34 MEDLINE

1998321225 Document Number: 98321225. PubMed ID: 9647791. Demonstration of receptors specific for **connective tissue**

**growth factor** on a human chondrocytic cell line

(HCS-2/8). Nishida T; Nakanishi T; Shimo T; Asano M; Hattori T;

**Tamatani T; Tezuka K; Takigawa M.** (Department

of Biochemistry and Molecular Dentistry, Okayama University Dental

School,

Japan. ) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Jun 29) 247 (3) 905-9. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB The presence of receptors specific for **connective tissue**

**growth factor** (CTGF) was demonstrated on a human

chondrosarcoma-derived chondrocytic cell line, HCS-2/8. The binding of <sup>125</sup>I-labeled recombinant CTGF to HCS-2/8 cells was inhibited by unlabeled CTGF but not by PDGF-BB or bFGF. Scatchard analysis revealed the presence

of two classes of binding sites with Kd values of 18.6 and 259 nM on cells. A cross-linking study revealed the formation of 125I-CTGF-receptor complex with an apparent molecular weight of 280 kDa. The 125I-CTGF-receptor complex disappeared almost completely on the addition of unlabeled CTGF but not PDGF-BB or bFGF. In addition, the 125I-CTGF-receptor complex was immunoprecipitated with anti-CTGF antiserum but not with anti-PDGF receptor antiserum. These findings suggest that CTGF directly binds to specific receptor molecules on HCS-2/8 cells.

L21 ANSWER 26 OF 34 MEDLINE

1999008896 Document Number: 99008896. PubMed ID: 9790981. Establishment of the enzyme-linked immunosorbent assay for **connective tissue growth factor** (CTGF) and its detection in the sera of biliary atresia. **Tamatani T**; Kobayashi H; **Tezuka K**; **Sakamoto S**; Suzuki K; Nakanishi T; **Takigawa M**; Miyano T. (Pharmaceutical Frontier Research Laboratories, JT Inc., Yokohama, Kanagawa, 236-0004, Japan.. tamatani@ikrl.jti.co.jp) . BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Oct 29) 251 (3) 748-52. Journal code: 9Y8; 0372516.

ISSN: 0006-291X. Pub. country: United States. Language: English.

AB **Connective tissue growth factor**

(CTGF) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine monoclonal antibodies against CTGF and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of CTGF. By using the ELISA, we confirmed that CTGF was specifically induced in human fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of CTGF were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that CTGF is potentially a useful

parameter for monitoring certain types of fibrotic disorders.  
Copyright 1998 Academic Press.

L21 ANSWER 27 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS

1999:459 Document No.: PREV199900000459. Establishment of the enzyme-linked immunosorbent assay for **connective tissue growth factor** (CTGF) and its detection in the sera of biliary atresia. **Tamatani, Takuya**; Kobayashi, Hiroyuki; **Tezuka, Katsunari**; **Sakamoto, Shinji**; Suzuki, Kensuke; Nakanishi, Tohru; **Takigawa, Masaharu**; Miyano, Takeshi. Pharmaceutical Frontier Res. Lab., JT Inc. 1-13-2 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004 Japan. Biochemical and Biophysical Research Communications, (Oct. 29, 1998) Vol. 25, No. 3, pp. 748-752. ISSN: 0006-291X. Language: English.

AB **Connective tissue growth factor**

(CTGF) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine monoclonal antibodies against CTGF and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of CTGF. By using the ELISA, we confirmed that CTGF was specifically induced in human fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of CTGF were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that CTGF is potentially a useful

parameter for monitoring certain types of fibrotic disorders.

L21 ANSWER 28 OF 34 CAPLUS COPYRIGHT 2001 ACS

1998:257383 Document No. 129:76530 CTGF, the most important factor for endochondral ossification. **Takigawa, Masaharu**; Nakanishi, Tohru; Shimo, Tsuyoshi (Dep. Oral Biochem., Okayama Univ. Sch. Dent., Japan). Saibo Kogaku, 17(3), 357-362 (Japanese) 1998. CODEN: SAKOEO. ISSN: 0287-3796. Publisher: Shujunsha.

AB A review with 23 refs., on cloning of **connective tissue growth factor** (CTGF); CTGF and CCN gene families; CTGF stimulation of chondrocyte proliferation and differentiation; and angiogenic effect of CTGF.

L21 ANSWER 29 OF 34 MEDLINE

1998309859 Document Number: 98309859. PubMed ID: 9644255. Inhibition of endogenous expression of **connective tissue growth factor** by its antisense oligonucleotide and antisense RNA suppresses proliferation and migration of vascular endothelial cells. Shimo T; Nakanishi T; Kimura Y; Nishida T; Ishizeki K; Matsumura T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry Iwate Medical University School of Dentistry,

Morioka, 020-0021, Japan. ) JOURNAL OF BIOCHEMISTRY, (1998 Jul) 124 (1) 130-40. Journal code: HIF; 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB Previously, we cloned an mRNA predominantly expressed in hypertrophic chondrocytes by differential display-PCR from a human chondrosarcoma-derived chondrocytic cell line (HCS-2/8) that is identical to that of **connective tissue growth factor**

(CTGF). In the present study, we investigated the roles of CTGF in the proliferation and migration of vascular endothelial cells using its antisense oligonucleotide and antisense RNA, because angiogenesis into

the hypertrophic zone of cartilage occurs at the final step of endochondral ossification. Immunohistochemical and immunofluorescence techniques revealed that not only hypertrophic chondrocytes but also endothelial cells in the cost-chondral junctions of mouse ribs were stained with an anti-CTGF antibody in vivo. Northern blot analysis revealed that CTGF was strongly expressed in chondrocytic cells as well as bovine aorta endothelial (BAE) cells in culture, but not in other types of cells such as osteoblastic cells. Its expression in BAE cells was greater in the growing phase than in the confluent phase. When one-half of a monolayer

of a confluent culture of BAE cells had been peeled off, only the cells proliferating and extending into the vacant area were stained with the anti-CTGF antibody. The addition of an antisense oligonucleotide inhibited

the proliferation and extension of the BAE cells into the vacant area.

The antisense oligonucleotide also inhibited the proliferation of BAE cells in

the rapidly proliferating phase. In a Boyden chamber assay, pretreatment with the antisense oligonucleotide markedly inhibited the migration of

BAE cells. Furthermore, the abilities to proliferate and migrate of BAE cells,

which were stably transfected with expression vectors that generate the antisense RNA of CTGF cDNA, were markedly lower than those of the control.

These findings suggest that endogenous CTGF expression is involved in the

proliferation and migration of BAE cells.

- L21 ANSWER 30 OF 34 SCISEARCH COPYRIGHT 2001 ISI (R)  
1998:408942 The Genuine Article (R) Number: ZK302. Possible roles of **connective tissue growth factor** (CTGF)-related gene in angiogenesis.. Endo T (Reprint); Nakanishi T; Kimura Y; Hatton T; Nishida T; Matsumura T; **Takigawa M.** OKAYAMA UNIV, SCH DENT, OKAYAMA 700, JAPAN. FASEB JOURNAL (31 JUL 1997) Vol. 11, No. 9, Supp. [S], pp. 3475-3475. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638. Pub. country: JAPAN. Language: English.
- L21 ANSWER 31 OF 34 SCISEARCH COPYRIGHT 2001 ISI (R)  
1998:406945 The Genuine Article (R) Number: ZK302. Cloning of a mRNA preferentially expressed in chondrocytes by differential display-PCR: Identity with **connective tissue growth factor** (CTGF) mRNA.. Nakanishi T (Reprint); Kimura Y; Tamura T; Ichikawa H; Yamaai Y; Sugimoto T; **Takigawa M.** OKAYAMA UNIV, SCH DENT, OKAYAMA 700, JAPAN. FASEB JOURNAL (31 JUL 1997) Vol. 11, No. 9, Supp. [S], pp. 1476-1476. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638. Pub. country: JAPAN. Language: English.
- L21 ANSWER 32 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS  
1997:422740 Document No.: PREV199799721943. Possible roles of **connective tissue growth factor** (CTGF)-related gene in angiogenesis. Endo, T.; Nakanishi, T.; Kimura, Y.; Hattori, T.; Nishida, T.; Matsumura, T.; **Takigawa, M.** Okayama Univ. Dent. Sch., Okayama Japan. FASEB Journal, (1997) Vol. 11, No. 9, pp. A1451. Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997 ISSN: 0892-6638. Language: English.
- L21 ANSWER 33 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS  
1997:420740 Document No.: PREV199799719943. Cloning of a mRNA preferentially expressed in chondrocytes by differential display-PCR: Identity with **connective tissue growth factor** (CTGF) mRNA. Nakanishi, T.; Kimura, Y.; Tamura, T.; Ichikawa, H.; Yamaai, Y.; Sugimoto, T.; **Takigawa, M.** Okayama Univ. Dental Sch., Okayama Japan. FASEB Journal, (1997) Vol. 11, No. 9, pp. A1109. Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997 ISSN: 0892-6638. Language: English.
- L21 ANSWER 34 OF 34 MEDLINE  
97312549 Document Number: 97312549. PubMed ID: 9168990. Cloning of a mRNA preferentially expressed in chondrocytes by differential display-PCR from a human chondrocytic cell line that is identical with **connective tissue growth factor** (CTGF) mRNA. Nakanishi T; Kimura Y; Tamura T; Ichikawa H; Yamaai Y; Sugimoto T; **Takigawa M** . (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Japan. ) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 May 8) 234 (1) 206-10. Journal code: 9Y8; 0372516.

ISSN: 0006-291X. Pub. country: United States. Language: English.  
AB Chondrocyte- or chondrosarcoma cell line (HCS)-specific DNA fragments  
were

obtained using differential display-PCR. Nucleotide sequences of 32  
species derived from HCS cells were determined. One of the sequence tags  
(tag no. 24) corresponded to the nucleotide sequence of **connective  
tissue growth factor** (CTGF). Northern blot  
analysis showed that CTGF was highly expressed in HCS cells and rabbit  
growth cartilage cells in culture but was not expressed in osteoblastic  
cells in culture. In situ hybridization revealed that CTGF was expressed  
only in the hypertrophic chondrocytes of costal cartilage and the  
vertebral column in embryonic mice. The expression of CTGF in HCS cells  
was up-regulated by the addition of TGF-beta or BMP-2. These findings  
suggest that CTGF participates in endochondral ossification.

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